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Cancer Incidence in Atomic Bomb Survivors. Part IV: Comparison of Cancer Incidence and Mortality

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This report compares cancer incidence and mortality among atomic bomb survivors in the Radiation Effects Research Foundation Life Span Study (LSS) cohort. Because the incidence data are derived from the Hiroshima and Nagasaki tumor registries, case ascertainment is limited to the time (1958–1987) and geographic restrictions (Hiroshima and Nagasaki) of the registries, whereas mortality data are available from 1950–1987 anywhere in Japan. With these conditions, there were 9,014 first primary incident cancer cases identified among LSS cohort members compared with 7,308 deaths for which cancer was listed as the underlying cause of death on death certificates. When deaths were limited to those occurring between 1958–1987 in Hiroshima or Nagasaki, there were 3,155 more incident cancer cases overall, and 1,262 more cancers of the digestive system. For cancers of the oral cavity and pharynx, skin, breast, female and male genital organs, urinary system and thyroid, the incidence series was at least twice as large as the comparable mortality series. Although the incidence and mortality data are dissimilar in many ways, the overall conclusions regarding which solid cancers provide evidence of a significant dose response generally confirm the mortality findings. When either incidence or mortality data are evaluated, significant excess risks are observed for all solid cancers, stomach, colon, liver (when it is defined as primary liver cancer or liver cancer not otherwise specified on the death certificate), lung, breast, ovary and urinary bladder. No significant radiation effect is seen for cancers of the pharynx, rectum, gallbladder, pancreas, nose, larynx, uterus, prostate or kidney in either series. There is evidence of a significant excess of nonmelanoma skin cancer in the incidence data, but not in the mortality series. Cancers of the salivary gland and thyroid are also in excess in the incidence series, but they were not evaluated in the earlier mortality analyses. For all solid tumors the estimated excess relative risk at 1 Sv ($ERR_{1\,Sv}$) for incidence ($ERR_{1\,Sv}$ = 0.63) is 40% larger than the excess relative risk (ERR) based on mortality data from 1950–1987 in all Japan ($ERR_{1\,Sv}$ = 0.45). The corresponding excess absolute risk (EAR) point estimate is 2.7 times greater for incidence than mortality. For some cancer sites, the difference in the magnitude of risk between incidence and mortality is greater. These differences reflect the greater diagnostic accuracy of the incidence data and the lack of full representation of radiosensitive but relatively nonfatal cancers, such as breast and thyroid, in the mortality data. Analyses of both incidence and mortality data are needed since the two end points provide complementary information for risk assessment.

INTRODUCTION

Over the past 40 years, the Atomic Bomb Casualty Commission (ABCC)[2] and later the Radiation Effects Research Foundation (RERF) have published many reports on cancer mortality among A-bomb survivors in the Life Span Study (LSS) [e.g., Preston *et al. (1),* Shimizu et al. *(2)*], but relatively few on cancer incidence. Recent improvements in the Hiroshima and Nagasaki tumor registries have made it possible to evaluate cancer incidence in the LSS cohort based on the tumor registry data *(3).* Because mortality data for the atomic bomb survivors have been the basis of virtually all previous risk estimates *(4–6),* a comparison between the incidence and mortality data and the risk estimates derived from them is warranted.

The present paper aims to (1) describe the differences in the incidence and mortality case series, (2) compare the

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[2] Abbreviations used: ABCC, Atomic Bomb Casualty Commission; AHS, Adult Health Study; AMFIT, Additive Multiplicative Fitting Program for analysis of data for cohort survival from *Epicure User's Guide* (see ref. *17);* AR, attributable risk; ATB, at the time of the bombings; DATAB, computer program from *Epicure User's Guide* (see ref. *17);* DS86, Dosimetry System 1986; EAR, excess absolute risk; ERR, excess relative risk; ICD-O, International Classification of Diseases—Oncology; LSS, Life Span Study; NIC, not in city; NOS, not otherwise specified; PY, person years; RBE, relative biological effectiveness; RERF, Radiation Effects Research Foundation.

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tumor registry diagnoses to the underlying cause of death on death certificates, and (3) evaluate the nature and magnitude of radiation effects and effect modifiers for the major cancer sites using incidence and mortality data. Since analysis of the LSS incidence data focuses on first primary cancers only *(3)*, we have limited the comparisons in this paper to first primary incident cancers also. As a consequence of this restriction, differences between tumor registry and death certificate diagnoses do not necessarily reflect death certificate inaccuracies.

MATERIALS AND METHODS

Study Population

This report is based on the 120,321 people belonging to the extended Life Span Study (LSS-E85) cohort of A-bomb survivors. This cohort has been studied frequently and is described in detail in the companion paper on cancer incidence *(3)* and in the comprehensive report on mortality from 1950–1982 *(1)*. The present study population constitutes a subset of the LSS-E85 sample. Excluded from the 120,321 in the LSS cohort are 26,580 people who were not in Hiroshima or Nagasaki (usually referred to as not in city or NIC) at the time of the bombings (ATB), 7,109 individuals who have unknown DS86 doses, and 263 persons with dose estimates above 4 Gy kerma *(3)*.

The follow-up of mortality started on October 1, 1950, and the follow-up of incidence began with the establishment of the tumor registries on January 1, 1958. For the analysis of mortality, 60 individuals whose vital status was unknown at the start of follow-up were excluded, leaving 86,309 (58.8% female) persons with a total of 2,588,874 person-years for study. For the analysis of incidence, 6,397 persons who had died or had a known cancer before 1958 were also excluded. Taking these restrictions into account, the incidence study population comprises 79,972 (59.6% female) persons with 1,950,567 person-years of follow-up. For the analysis of both incidence and mortality, the closing date was December 31, 1987.

Slightly over 50% of both the incidence and mortality study populations had a DS86 total kerma estimate of less than 0.01 Gy. These people are considered a comparison population, sometimes referred to as nonexposed subjects in this report. Survivors with DS86 total kerma estimates of more than 0.01 Gy are referred to as the exposed group. By the end of the follow-up period, 11.3% of the incidence study population had developed cancer, 8.5% of the mortality cohort had died of cancer, and in total 37.5% had died of any cause.

Cancer Ascertainment

Incident cancer cases are routinely identified by computer linkage between the LSS cohort and the LSS tumor registries supplemented by manual searches *(3, 7)*. Because the Hiroshima and Nagasaki tumor registries were not established until 1958, complete ascertainment of solid tumors is possible only from that time forward. However, a special registry of leukemia, lymphoma and multiple myeloma, as well as other, nonmalignant, hematopoietic disorders, covers cases diagnosed since 1948 *(8)*. Deaths are identified regularly through the compulsory Japanese family registration (Koseki) system and cause of death as stated on the death certificate is obtained for deceased LSS members *(1, 2)*.

Incident cancers are coded according to the guidelines of the International Classification of Diseases for Oncology (ICD-O) *(9)*, whereas deaths are coded according to the ICD revision *(10–12)* in effect at the time of death. For this paper, the cancer causes of death from the death certificates were recoded so that the diagnoses would be compatible with the incidence data. Included in the cancer incidence category were first primary malignant tumors (ICD-O 140–199; behavior code 3), as well as brain and nervous system tumors of uncertain or benign behavior (ICD-O 191 and 192; behavior codes 0 and 1). As in the standard LSS mortality reports, cases for the mortality analyses were restricted to deaths with cancer (ICD-O codes as described above) listed as the underlying cause of death on the death certificate.

Based on data from the RERF Adult Health Study (AHS), a subset of the LSS invited for biennial clinical examinations, about 20% of the surviving members of the LSS cohort were estimated to have migrated from Hiroshima and Nagasaki by 1980. Since these migrants would not be in the LSS tumor registry catchment area, cases were restricted to persons who were Hiroshima or Nagasaki residents at the time of diagnosis. Statistical procedures developed by Sposto and Preston *(13)* were used to adjust the person-years of observation for migration. Analogous methods were used when geographic restrictions were applied to the mortality data.

Dosimetry

Estimates of individual γ-ray and neutron kerma and organ doses were computed using the 1989 version of the DS86, which incorporates various minor changes and allows the computation of estimates for 10,539 additional survivors *(14, 15)* not used in previous analyses of mortality *(2, 16)*.

Organ equivalent doses were calculated as the sum of the DS86 γ–radiation dose and ten times the neutron dose, i.e., a constant relative biological effectiveness (RBE) of ten for neutrons was assumed. As in the other papers in this series *(3, 8)*, equivalent doses computed in this way are expressed in sieverts. Analyses for specific types of cancer were based on the equivalent dose to the most appropriate organ chosen from the 15 organ doses available in DS86. For the oral cavity, nasopharynx and skin, which are close to the body surface, shielded kerma was taken as an estimate of the organ dose because DS86 does not provide skin dose estimates. For hematopoietic and lymphatic tumors, bone marrow dose estimates were used. As in the report on solid cancer *(3)*, individuals with kerma over 4 Gy were excluded because their doses are implausible and likely to be inaccurate.

Statistical Analysis

In contrast to the incidence data, mortality data cover the entire country from 1950 on. Therefore, we defined four data series: (1) incidence in Hiroshima and Nagasaki between 1958–1987 (as used in the report on solid tumor incidence) *(3)*; (2) mortality in Hiroshima and Nagasaki between 1958–1987 (so that the incidence and mortality data would be comparable); (3) mortality anywhere in Japan between 1958–1987 (so that the impact of migration could be assessed); and (4) mortality anywhere in Japan between 1950–1987 (so that the first 8 years of follow-up could be assessed and because mortality data without time and geographic restrictions are used in the standard LSS reports). Various mortality series were used depending on the questions addressed.

To compare the incidence and mortality data, the distribution of cases for specific cancer types and/or organ systems stratified by potential effect modifiers was determined in the four series. Agreement between the diagnosis coded as the first primary cancer in the tumor registry and the underlying cause of death shown on the death certificate also was assessed.

Radiation risk estimates were obtained from incidence and mortality data using Poisson regression methods. These methods have been described in more detail in the companion reports on cancer incidence *(3, 8)*. For each diagnosis, analyses were based on a tabulation of case counts and person-years stratified by age at exposure (13 categories), DS86 organ dose (10 categories), calendar time (7 categories for incidence and 9 categories for mortality), sex and city. Follow-up continued from either October 1, 1950, or January 1, 1958, depending on the data series, until the earliest of the date of first primary cancer (incidence series only), date of death or December 31, 1987. In addition to the number of person-years and case counts, the covariates computed for each cell included person-year weighted mean values of age at exposure,

TABLE 1
Distribution of LSS Cancer Cases and Deaths by Sex and Selected Exposure Characteristics

	Incidence	Mortality		
	1958–1987 Hiroshima and Nagasaki	1958–1987 Hiroshima and Nagasaki	1958–1987 All Japan	1950–1987 All Japan
People	79,972	80,114	80,114	86,309
Person years	1,950,567	1,983,620	1,983,620	2,588,874
Malignancies	9,014	5,859	6,343	7,308
Sex				
Female	5,039 (55.9%)	3,065 (52.3%)	3,333 (52.5%)	3,806 (52.1%)
Male	3,975 (44.1%)	2,794 (47.7%)	3,010 (47.5%)	3,502 (47.9%)
Age at exposure				
0–9	390 (4.3%)	143 (2.4%)	191 (3.0%)	203 (2.8%)
10–19	1,053 (11.7%)	473 (8.1%)	563 (8.9%)	583 (8.0%)
20–29	1,191 (13.2%)	629 (10.7%)	693 (10.9%)	729 (10.0%)
30–39	2,116 (23.5%)	1,395 (23.8%)	1,479 (23.3%)	1,568 (21.5%)
40–49	2,629 (29.2%)	1,952 (33.3%)	2,073 (32.7%)	2,345 (32.1%)
50–59	1,313 (14.6%)	1,033 (17.6%)	1,095 (17.3%)	1,400 (19.2%)
60+	322 (3.6%)	234 (4.0%)	249 (3.9%)	480 (6.6%)
City of exposure				
Hiroshima	6,557 (72.7%)	4,267 (72.8%)	4,555 (71.8%)	5,259 (72.0%)
Nagasaki	2,457 (27.3%)	1,592 (27.2%)	1,788 (28.2%)	2,049 (28.0%)
Radiation dose (Gy)				
<0.01	4,485 (49.8%)	2,941 (50.2%)	3,143 (49.6%)	3,635 (49.7%)
0.01–0.99	4,167 (46.2%)	2,752 (47.0%)	2,968 (46.8%)	3,409 (46.6%)
>1.00	362 (4.0%)	166 (2.8%)	232 (3.7%)	264 (3.6%)

attained age and organ dose (γ rays, neutrons and total). The tables were constructed using the DATAB *(17)* software program.

The main analyses were based on general excess relative risk (ERR) models, however, time-dependent excess absolute risk (EAR) models were also considered. Background rates were modeled as a function of city, sex, attained age and year of birth. The effect modifiers included city, sex, attained age, time since exposure and age since exposure. The linear dose–response function, $p(d) = \gamma_i d$, where d is the equivalent dose in sieverts assuming an RBE of 10, was used as the standard model. Nonlinearity in the dose response, based on a linear–quadratic dose–response model, was also tested. The standard effect-modification tests were based on a dose–effect modification function of the form $\varepsilon(z)e^{\theta z}$, where θ is a vector of parameters and z is a covariate vector that included one or more of the following covariates: a sex indicator, age at exposure, log time since exposure, log attained age and a city indicator for Hiroshima and Nagasaki. Temporal effects in ERR models were tested with and without adjustment for the effects of age at exposure on the excess risk.

Parameter estimates were computed using maximum-likelihood methods for grouped survival data. Hypothesis tests were based on likelihood-ratio tests where possible, and on score tests otherwise. Confidence bounds were computed from the profile likelihood function *(18)*. AMFIT *(17)* was used for estimation and the computation of test statistics.

RESULTS

Incidence and Mortality Case Series

Between 1958–1987 9,014 patients had primary incident cancers diagnosed in Hiroshima and Nagasaki. Among these patients, 460 had 2 or more primary cancers, yielding a total of 9,508 primary cancers. The most common sites for a second primary were stomach, lung and colon.

Compared to the 9,014 first primaries included in the cancer incidence analyses, there were 7,308 deaths in which cancer was listed as the underlying cause of death when the complete mortality data were used i.e., for the period 1950–1987 anywhere in the country (Table I). When the mortality series is restricted to the 1958–1987 follow-up period, the number of deaths is reduced by 965 (13%). Another 484 (8%) deaths are lost when mortality is further limited to Hiroshima and Nagasaki. All together 1,449 deaths occurred between 1950 and 1958 or outside of Hiroshima and Nagasaki. Yet the three mortality series were remarkably alike in terms of distribution by sex, age at exposure, city of exposure and radiation dose. A comparison between incidence and mortality cancer cases showed that the incidence series had a higher proportion of females and persons exposed to the bombings before age 30, whereas there was no difference in city of exposure or radiation dose.

The three mortality series are also quite similar in terms of their distribution by cancer site (Table II). Digestive system cancers constitute 60% of the cancers, respiratory system cancers 13–14%, female genital system cancers 7–8%, other and ill-defined solid cancers 4%, and hematopoietic malignancies and lymphomas 6% in the three series.

With the same time and geographic restrictions, the incident cancer series included 3,155 more cases than deaths from cancer (Table II). For the total digestive system there were 1,262 more cases in the incidence series than the comparable mortality series. For cancers of the oral cavity and

TABLE II
Distribution of LSS Cancer Cases and Deaths by Site or Organ System

	Incidence	Mortality		
	1958–1987 Hiroshima and Nagasaki	1958–1987 Hiroshima and Nagasaki	1958–1987 All Japan	1950–1987 All Japan
All tumors	9,014 (100.0%)	5,859 (l00.0%)	6.343 (100.0%)	7,308 (100.0%)
Solid tumor total	8,612 (95.5%)	5,529 (94.4%)	5.988 (94.4%)	6,887 (94.2%)
Oral cavity	132 (1.5%)	67 (1.1%)	70 (1.1%)	79 (1.1%)
Digestive system	4,796 (53.2%)	3,534 (60.3%)	3,803 (60.0%)	4,408 (60.3%)
Esophagus	184[a]	174	180	211
Stomach	2,658	1,843	1,985	2,365
Colon	457	240	260	277
Rectum	351	219	241	273
Liver	585	610	656	761
Gallbladder	295	170	185	187
Pancreas	240	215	229	243
Other	26	63	67	91
Respiratory system	1,027 (11.4%)	828 (14.1%)	895 (14.1%)	941 (12.9%)
Nasal	55	41	42	51
Larynx	80	39	42	52
Lung	872	730	791	816
Other respiratory	20	18	20	22
Skin	18l (2.0%)	29 (0.5%)	31 (0.5%)	36 (0.5%)
Melanoma	13	6	8	8
Other skin	168	13	23	28
Female breast	529 (5.9%)	142 (2.4%)	159 (2.5%)	186 (2.5%)
Female genital	891 (9.9%)	402 (6.9%)	456 (7.2%)	575 (7.9%)
Cervix	553	85	95	110
Corpus	85	14	15	15
Uterus NOS	86	203	234	315
Ovary	133	82	93	104
Other	34	18	19	31
Male genital	160 (1.8%)	68 (1.2%)	72 (1.1%)	75 (1.0%)
Prostate	140	63	67	69
Other	20	5	5	6
Urinary system	325 (3.6%)	130 (2.2%)	142 (2.2%)	156 (2.1%)
Urinary bladder	210	84	92	104
Kidney	73	39	43	45
Renal pelvis and ureter	28	4	4	4
Other	14	3	3	3
Nervous system	125 (1.4%)	55 (0.9%)	59 (0.9%)	75 (1.0%)
Brain	55	51	55	71
CNS	70	4	4	4
Thyroid	225 (2.5%)	43 (0.7%)	47 (0.7%)	49 (0.7%)
Other solid cancers	221 (2.5%)	231 (3.9%)	254 (4.0%)	307 (4.2%)
Hemato-lymphopoietic	402 (4.5%)[b]	330 (5.6%)	355 (5.6%)	421 (5.8%)
Leukemia	170	163	178	230
Malignant lymphoma	174	128	l36	149
Multiple myeloma	58	39	41	42

[a] One case of esophageal cancer used in the solid tumor incidence report was subsequently found to have had an earlier diagnosis of malignant lymphoma, and therefore there is one less case of esophageal cancer than is reported in the companion paper *(3)*.

[b] Because of additional data sources for the hemato-lymphopoietic tumors, incidence data for these tumors are available from 1950 through 1987. Thus the analyses of leukemia, lymphoma and multiple myeloma incidence as described in ref. *(8)* were based on all 481 cases diagnosed between 1950 and 1987.

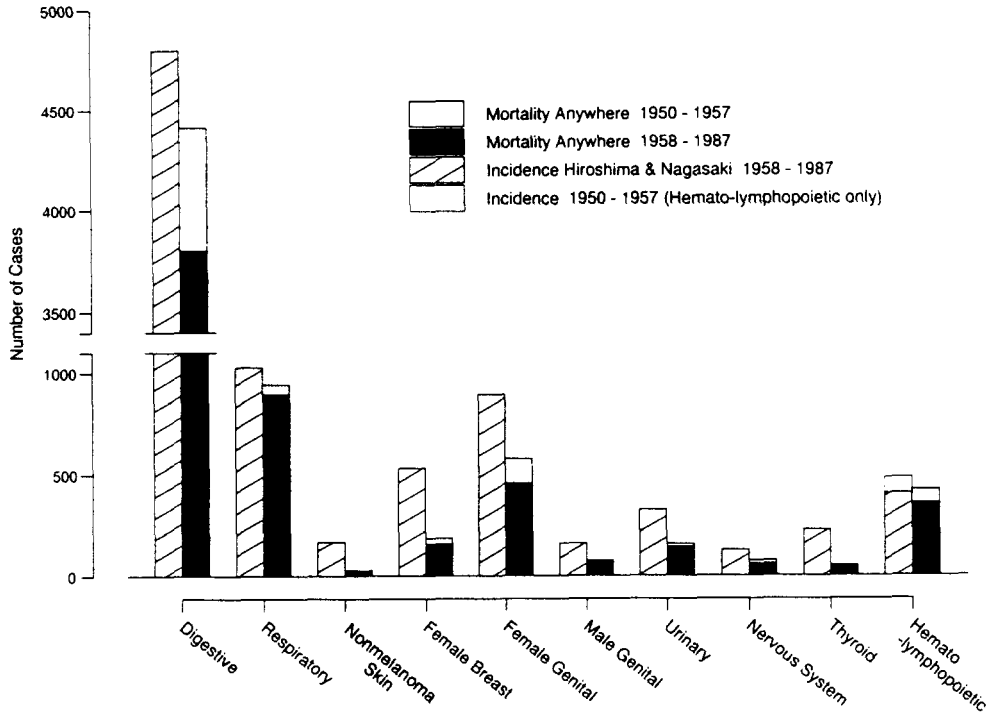

FIG. 1. Comparison of incidence and mortality data in the LSS cohort. The bar heights indicate the number of deaths and number of cancer cases by organ system. Data on mortality and hemato-lymphopoietic cancer incidence during the period from 1950 to 1987 are shown.

pharynx, skin, female breast, female and male genital system, urinary system and thyroid, the incidence series was at least twice as large as the comparable mortality series. The greatest difference was for nonmelanoma skin cancer; 23 deaths occurred in the mortality series compared with 168 cases in the incidence series. In contrast, using the mortality data there were 25 more liver cancers and 10 more cancers of ill-defined sites than in the incidence series, probably a reflection of less accurate diagnoses in the mortality data.

Figure 1 illustrates the comparison between the incidence series and the two geographically unrestricted mortality series. The smallest relative difference between incidence and mortality was for respiratory cancers and hematopoietic and lymphatic tumors. Before 1958, 605 digestive cancers, 119 female genital system cancers, and 66 hematopoietic and lymphatic fatal cancers developed.

Tumor Registry Diagnoses and Death Certificate Causes of Death

To understand better how the LSS cancer incidence and mortality reports differ, we compared the diagnoses from the tumor registry for first primary incident cancers and underlying causes of death on death certificates. For many sites studied, more than 50% of first primary incident cancer cases would have been missed or classified differently if only death certificates were used (Table III). The difference in the two data sets is due to the relatively large number of nonfatal cancer cases, deaths due to noncancer causes, the inclusion of first primaries only in the incidence data, and misclassification of the underlying cause of death.

Twenty-three percent of the 9,014 persons with first primary incident cancers were still alive at the end of follow-up and therefore would not be included in a mortality analysis. This figure varied from less than 10% for the cancers with poor survival rates (esophagus, liver, gallbladder, pancreas and lung) to over 50% for cancers with good survival rates (nonmelanoma skin, breast and thyroid cancer) (Table III). Another 14% had a noncancer coded as the underlying cause of death, which would also preclude their inclusion in studies based on death certificates. Over 30% of the nonmelanoma skin and prostate cancer patients had noncancer coded on their death certificates. Again, variation by site was wide and was correlated with survival patterns. Combining the alive and noncancer death categories, 37% of the cancers identified using incidence data would have been missed using mortality data. However, about 1,400 persons who died with cancer listed as the underlying cause of death outside of Hiroshima and Nagasaki or who died before 1958 are lost when the incidence data are used. These numbers are an approximation because some of the cases classified as dying from cancer on the death certificate would be misclassified.

TABLE III
Agreement between Tumor Registry and Death Certificate Diagnoses, 1958–1987

Tumor registry diagnosis	Primary cause on death certificate: Same cancer	Other cancer	Noncancer	Alive in 1988
Oral cavity	43.2%	12.1%	16.7%	28.0%
Esophagus	78.8%	6.5%	9.2%	5.4%
Stomach	65.1%	4.8%	12.5%	17.6%
Colon	44.2%	8.5%	12.7%	34.6%
Rectum	53.0%	7.1%	12.8%	27.1%
Liver	79.8%	3.6%	9.6%	7.0%
Gallbladder	52.2%	24.7%	16.3%	6.8%
Pancreas	72.1%	15.8%	7.5%	4.6%
Other gastrointestinal	50.0%	34.6%	11.5%	3.8%
Nasal	61.8%	5.5%	10.9%	21.8%
Larynx	45.0%	13.8%	18.8%	22.5%
Lung	73.9%	4.2%	14.4%	7.5%
Other respiratory	35.0%	45.0%	10.0%	10.0%
Melanoma	30.8%	15.4%	23.1%	30.8%
Other skin	7.1%	9.5%	32.7%	50.6%
Female breast	24.6%	4.7%	11.5%	59.2%
Cervix	14.5%	27.7%	13.2%	44.7%
Corpus	14.1%	25.9%	10.6%	49.4%
Uterus	60.5%	10.5%	5.8%	23.3%
Ovary	49.6%	17.3%	12.0%	21.1%
Other female genital	29.4%	23.5%	23.5%	23.5%
Prostate	36.4%	7.1%	38.6%	17.9%
Other male genital	25.0%	5.0%	30.0%	40.0%
Urinary bladder	34.3%	11.4%	25.2%	29.0%
Kidney	46.6%	9.6%	21.9%	21.9%
Other urinary tumors	14.3%	19.0%	19.0%	47.6%
Brain and CNS	35.2%	1.6%	27.2%	36.0%
Thyroid	16.4%	7.6%	20.4%	55.6%
Other solid tumors	46.2%	26.7%	12.7%	14.5%
Lympho-hematopoietic cancers (1950–1987)				
Leukemia	82.2%	8.0%	5.2%	4.6%
Malignant lymphoma	54.7%	9.4%	16.5%	19.4%
Multiple myeloma	58.6%	1.7%	12.1%	27.6%

TABLE IV
Detailed Comparison of Tumor Registry and Death Certificate Diagnoses by Organ System

Incidence	Oral cavity	Digestive system	Respiratory system	Skin	Female breast	Female genital system	Mortality: Male genital system	Urinary system	Nervous system	Thyroid	Other solid tumors	Lympho-hematopoietic cancers	Subtotal	Alive in 1988	Noncancer	Total
1958–1987 eligible cases																
Oral Cavity	57	1	6	1	0	0	0	0	0	0	6	2	73	37	22	132
Digestive system	1	3,322	29	3	0	9	2	0	2	0	40	6	3,414	804	578	4,796
Respiratory system	4	18	732	0	0	0	1	0	1	2	19	4	781	97	149	1,027
Skin	0	7	1	16	0	1	0	0	0	0	7	2	34	89	58	181
Female breast	0	11	6	1	130	3	0	0	0	0	3	1	155	313	61	529
Female genital system	0	28	13	2	1	370	0	5	0	1	15	0	435	345	111	891
Male genital system	0	1	4	0	0	0	56	2	0	0	1	3	67	33	60	160
Urinary system	0	13	5	0	0	2	3	117	0	1	8	2	151	97	77	325
Nervous system	0	1	0	0	0	0	0	0	44	0	0	1	46	45	34	125
Thyroid	0	5	5	0	0	1	0	0	0	37	6	0	54	125	46	225
Other solid tumor	1	33	11	3	0	2	2	1	2	0	103	4	162	31	28	221
Lympho-hemato-poietic cancers	0	9	1	0	1	1	0	0	0	0	4	285	301	57	44	402
Subtotal eligible cases	63	3,449	813	26	132	389	64	125	49	41	212	310	5,673	2,073	1,268	9,014
1958–1987 ineligible cases																
Noncancer	0	76	14	0	0	6	3	4	7	0	19	5	134	0	0	134
Benign or occult	0	6	2	1	0	0	0	0	1	0	0	0	10	123	154	287
Nonresident	4	201	54	1	14	38	3	9	1	3	11	27	366	0	22	388
Subtotal ineligible cases	4	283	70	2	14	44	6	13	9	3	30	32	510	123	176	809
1950–1957 all cases	12	676	58	8	40	142	4	18	17	5	66	79	1,125	0	8	1,133
Total 1950–1987	79	4,408	941	36	186	575	74	156	75	49	308	421	7,308	2,196	1,452	10,956

TABLE V
Detailed Comparison of Tumor Registry and Death Certificate Data for Gastrointestinal Cancers

	Mortality												
Incidence	Esophagus	Stomach	Colon	Rectum	Liver	Gallbladder	Pancreas	Other gastrointestinal	Other cancer	Subtotal	Alive in 1988	Noncancer	Total
1958–1987 eligible cases													
Esophagus	145	5	1	0	0	0	1	1	4	157	10	17	184
Stomach	20	1,730	4	6	28	4	10	14	41	1,857	468	333	2,658
Colon	1	6	202	15	5	0	1	0	11	241	158	58	457
Rectum	0	3	8	186	5	0	0	3	6	211	95	45	351
Liver	0	5	0	0	467	1	5	0	10	488	41	56	585
Gallbladder	0	8	1	0	41	154	7	4	12	227	20	48	295
Pancreas	1	15	0	0	9	4	173	3	6	211	11	18	240
Other gastrointestinal	1	0	4	0	1	0	1	13	2	22	1	3	26
Other cancer	2	31	15	9	31	9	9	21	2,132	2,259	1,269	690	4,218
Subtotal eligible cases	170	1,803	235	216	587	172	207	59	2,224	5,673	2,073	1,268	9,014
1958–1987 ineligible cases													
Noncancer	2	27	6	1	23	3	11	3	58	134	0	0	134
Benign or occult	1	5	0	0	0	0	0	0	4	10	123	154	287
Nonresident	3	108	19	11	38	10	10	2	165	366	0	22	388
Subtotal ineligible cases	6	140	25	12	61	13	21	5	227	510	123	176	809
1950–1957 all cases	35	422	17	45	113	2	15	27	449	1,125	0	8	1,133
Total 1950–1987	211	2,365	277	273	761	187	243	91	2,900	7,308	2,196	1,452	10,956

When cancer patients had a cancer diagnosis coded on their death certificate, agreement between the tumor registry and death certificate diagnoses was 93% (5,269/5,672) at the organ system level. Of the 3,732 persons who were classified as having died from cancer of the digestive system from 1958–1987, 201 (5.4%) were not resident in Hiroshima or Nagasaki and only 209 (5.6%) were classified as not having cancer or having a different cancer when their records were reviewed by the tumor registries. The corresponding data for the respiratory system were 54 (6.1%) nonresidents and 97 (11%) noncancers or cancers of other organ systems (Table IV). However, for some of the specific diagnoses, agreement was considerably poorer. For example, for colon, liver and pancreatic cancers coded as the underlying cause of death and fitting the time and geographic restrictions of the tumor registry, less than 80% had the same diagnosis in the tumor registry (Table V). Table VI compares mortality and incidence data for specific female genital organs and shows that death certificates are poor sources of information on subsites within the uterus.

TABLE VI
Detailed Comparison of Tumor Registry and Death Certificate Data for Cancers of the Female Genital Organs

	Mortality									
Incidence	Cervix	Uterus corpus	Uterus NOS	Ovary	Other female	Other cancer	Subtotal	Alive in 1988	Noncancer	Total
1958–1987 eligible cases										
Cervix	80	0	113	3	1	36	233	247	73	553
Uterus corpus	0	12	16	0	1	5	34	42	9	85
Uterus NOS	0	0	52	0	5	4	61	20	5	86
Ovary	0	1	5	66	0	17	89	28	16	133
Other female cancer	1	0	4	0	10	3	18	8	8	34
Other cancer	3	1	4	11	0	5,219	5,238	1,728	1,157	8,123
Subtotal eligible cases	84	14	194	80	17	5,284	5,673	2,073	1,268	9,014
1958–1987 ineligible cases										
Noncancer	0	0	3	2	1	128	134	0	0	134
Benign or occult	0	0	0	0	0	10	10	123	154	287
Nonresident	6	1	21	9	1	328	366	0	22	388
Subtotal ineligible cases	6	1	24	11	2	466	510	123	176	809
1950–1957 all cases	20	0	97	13	12	983	1,125	0	8	1,133
Total 1950–1987	110	15	315	104	31	6,733	7,308	2,196	1,452	10,956

TABLE VII
Summary of Risk Estimates by Cancer Site or Organ System

Cancer site organ system	Incidence Hiroshima and Nagasaki, 1958–1987			Mortality All Japan, 1950–1987			Mortality All Japan, 1958–1987		
	ERR$_{1\ Sv}$	EAR per 10,000 PY Sv	AR%	ERR$_{1\ Sv}$	EAR per 10,000 PY Sv	AR%	ERR$_{1\ Sv}$	EAR per 10,000 PY Sv	AR%
Total solid tumors	0.63 (0.52–0.74)[a]	29.7 (24.7–34.8)	11.6 (10.2–14.3)	0.45 (0.34–0.57)	11.1 (8.4–14.0)	9.0 (6.8–11.1)	0.46 (0.34–0.58)	12.4 (9.3–15.7)	9.1 (6.9–11.4)
Oral cavity and pharynx	0.29 (-0.09–0.93)	0.23 (-0.08–0.65)	9.1 (-3.0–25.9)	-0.16 (<-0.16–0.26)	-0.05 (<-0.05–0.08)	-5.5 (<-5.5–8.06)	-0.16 (<-0.16–0.32)	-0.06 (<-0.06–0.11)	-5.6 (<-5.6–9.9)
Digestive system	0.38 (0.25–0.52)	10.4 (7.0–14.0)	7.8 (5.3–10.6)	0.32 (0.19–0.46)	5.1 (3.0–7.3)	6.5 (3.9–9.1)	0.32 (0.18–0.46)	5.6 (3.2–8.1)	6.5 (3.8–9.3)
Esophagus	0.28 (-0.21–1.04)	0.30 (-0.23–1.0)	6.5 (-5.0–22.5)	0.60 (0.0–1.44)	0.45 (0.0–1.00)	11.6 (0.4–24.0)	0.49 (-0.1–0.37)	0.42 (-0.1–1.1)	9.8 (–2.1–23)
Stomach	0.32 (0.16–0.50)	4.8 (2.5–7.4)	6.5 (3.5–10.5)	0.22 (0.057–0.40)	1.9 (0.51–3.5)	4.7 (1.3–8.3)	0.21 (0.046–0.40)	2.0 (0.45–3.8)	4.6 (1.0–8.4)
Colon	0.72 (0.29–1.3)	1.8 (0.74–3.0)	14.2 (5.9–23.9)	0.52 (0.06–1.2)	0.51 (0.06–1.1)	10.1 (1.3–20.2)	0.57 (0.09–1.3)	0.64 (0.11–1.3)	11.1 (1.9–21.4)
Liver	0.49 (0.16–0.92)	1.6 (0.54–2.9)	10.9 (3.6–19.4)	0.46[b] (0.18–0.81)	1.3[b] (0.52–2.2)	10.0[b] (4.1–16.3)	0.50[b] (0.19–0.88)	1.5[b] (0.60–2.5)	10.7[b] (4.4–17.5)
Respiratory system	0.80 (0.50–1.2)	4.4 (2.9–6.1)	16.3 (10.6–22.6)	0.60 (0.31–0.94)	2.0 (1.1–3.0)	12.8 (7.1–18.8)	0.63 (0.34–0.99)	2.5 (1.4–3.7)	13.5 (7.7–19.6)
Trachea, bronchus and lung	0.95 (0.60–1.4)	4.4 (2.9–6.0)	18.9 (12.5–26.0)	0.65 (0.34–1.0)	1.9 (1.0–2.9)	13.8 (7.7–20.3)	0.67 (0.35–1.1)	2.3 (1.3–3.5)	14.3 (8.1–20.8)
Nonmelanoma skin	1.0 (0.41 –1. 9)	0.84 (0.40–1.4)	24.1 (11.5–38.6)	0.31 (<-0.15–1.8)	0.034 (<-0.019–0.16)	8.9 (<-5.2–36.5)	0.42 (-0.15–2.2)	0.049 (-0.019–0.20)	11.8 (-5.0–41.5)
Female breast	1.6 (1.1–2.2)	6.7 (4.9–8.7)	31.9 (23.2–41.1)	1.3 (0.57–2.3)	1.3 (0.64–2.1)	26.5 (13.7–39.2)	1.5 (0.66–2.6)	1.6 (0.78–2.5)	29.0 (0.16–0.42)
Uterus	-0.15 (-0.29–0.10)	-1.1 (-2.1–0.68)	-3.3 (-6.4–2.1)	0.10 (-0.22–0.55)	0.26 (-0.60–1.4)	2.0 (-4.8–10.3)	0.044 (-0.26–0.51)	0.12 (-0.73–1.3)	0.93 (-5.9–9.8)
Ovary	0.99 (0.12–2.3)	1.1 (0.15–2.3)	17.7 (2.4–37.3)	1.2 (0.18–2.8)	0.69 (0.12–1.4)	20.3 (3.8–37.7)	1.4 (0.28–3.2)	0.90 (0.21–1.8)	23.2 (5.8–41.1)
Prostate	0.29 (-0.21–1.2)	0.61 (-0.46–2.2)	7.0 (-5.3–25.5)	0.25 (<0.26–1.6)	0.16 (<0.18–0.87)	5.6 (<-6.5–26.6)	0.28 (<-0.26–1.6)	0.21 (<-0.21–1.1)	6.1 (<-6.6–27.5)
Urinary organs and kidney	1.2 (0.62–2.1)	2.1 (1.1–3.2)	22.3 (11.8–34.2)	1.3 (0.42–2.6)	0.67 (0.24–1.2)	22.4 (8.6–36.6)	1.3 (0.44–2.7)	0.79 (0.29–1.4)	23.2 (9.0–37.6)
Urinary bladder	1.0 (0.27–2.1)	1.2 (0.34–2.1)	16.3 (4.8–30.1)	1.5 (0.29–3.3)	0.49 (0.11–0.94)	23.9 (6.0–41.8)	1.5 (0.29–3.4)	0.56 (0.13–1.1)	24.4 (6.1–42.6)
Nervous system	0.26 (-0.23–1.3)	0.19 (-0.17–0.81)	5.7 (-5.3–24.5)	0.43 (<-0.23–2.0)	0.12 (<-0.069–0.46)	10.2 (<-6.4–34.6)	0.61 (<-0.23–2.5)	0.17 (<-0.070–0.55)	13.9 (<-6.4–39.6)
Thyroid	1.2 (0.48–2.1)	1.6 (0.78–2.5)	25.9 (12.4–40.7)	0.094 (-0.23–1.7)	0.016 (-0.04–0.24)	2.3 (-6.1–30.1)	0.016 (-0.23–1.5)	0.0032 (-0.048–0.26)	0.40 (-6.2–27.7)

[a] 95% confidence interval.
[b] Includes all liver cancer coded on the death certificate as primary or NOS

Radiation Effects for Solid Tumors Using Incidence and Mortality Data

To compare radiation effects in the incidence and mortality series, we limited our analyses to solid tumors because the risk patterns for hematopoietic and lymphatic tumors are different from those for solid tumors, and we felt it would be inappropriate to combine the two tumor groups. Furthermore, comparisons between incident and fatal hematopoietic and lymphatic tumors are included in the companion paper devoted to these tumors *(8)*. An evaluation of risk estimates, using ERR, EAR or attributable risk (AR)%, indicates that the two mortality series without geographic restrictions are quite similar (Table VII), although the point estimates are slightly lower for most cancer sites in the series with follow-up starting in 1950. Since there was no appreciable difference between the two mortality series, we describe the results for the incidence and mortality comparisons based on the mor-

TABLE VIII
LSS Solid Tumor Deaths 1950–1987
Distribution of Observed and Fitted Deaths by Sex, Time Period, Exposure Status and Age at Exposure

		1950–1957		1958–1975		1976–1987		1950–1987	
Age at exposure	Dose category	<0.01 Gy	0.01–4 Gy	<0.01 Gy	0.01–4 Gy	<0.01 Gy	0.01–4 Gy	<0.01 Gy	0.01–4 Gy
				Males					
0–19	Observed cases	3	3	29	44	131	138	163	185
	Fitted background	0.58	0.54	32.48	28.89	139.23	120.32	172.28	149.75
	Fitted excess	0.00	0.16	0.03	4.68	0.14	18.74	0.17	23.51
20–39	Observed cases	11	13	158	137	262	256	4.31	406
	Fitted background	17.28	15.28	158.84	140.56	231.49	206.78	407.62	362.62
	Fitted excess	0.01	1.38	0.07	12.83	0.11	19.26	0.19	33.46
40+	Observed cases	225	202	615	593	247	230	1087	1025
	Fitted background	243.54	219.09	609.63	562.58	236.94	222.90	1090.11	1004.58
	Fitted excess	0.07	9.91	0.20	29.97	0.09	12.47	0.36	52.35
All ages	Observed cases	239	218	802	774	640	624	1681	1616
	Fitted background	261.40	234.91	800.95	732.03	607.67	550.00	1670.02	1516.95
	Fitted excess	0.08	11.38	0.30	47.47	0.33	50.46	0.72	109.32
				Females					
0–19	Observed cases	4	1	51	49	103	125	158	175
	Fitted background	3.08	2.55	52.24	43.20	134.63	110.47	189.96	150.23
	Fitted excess	0.00	0.69	0.09	11.66	0.24	29.49	0.33	41.84
20–39	Observed cases	47	40	237	290	332	375	616	705
	Fitted background	35.21	32.92	249.15	231.85	368.86	338.96	653.23	603.73
	Fitted excess	0.04	4.56	0.27	32.97	0.41	48.70	0.72	86.22
40+	Observed cases	178	172	542	534	260	250	980	956
	Fitted background	185.03	157.58	515.53	445.80	258.90	227.16	959.46	830.54
	Fitted excess	0.11	10.75	0.36	35.77	0.20	20.55	0.67	67.07
All ages	Observed cases	229	213	830	873	695	750	1754	1836
	Fitted background	223.32	193.05	816.93	720.86	762.39	676.59	1802.64	1590.50
	Fitted excess	0.16	15.99	0.72	80.40	0.85	98.74	1.72	195.13
				Both sexes					
All ages	Observed cases	468	431	1632	1647	1335	1374	3435	3452
	Fitted background	484.72	427.96	1617.88	1452.89	1370.06	1226.59	3472.66	3107.45
	Fitted excess	0.24	27.38	1.02	127.87	1.18	149.20	2.44	304.45

tality series most similar to that used in the LSS reports (All Japan, 1950–1987).

For all solid tumors the estimated ERR for incidence ($ERR_{1\,Sv} = 0.63$) is 40% larger than that based on mortality data ($ERR_{1\,Sv} = 0.45$). Further examination reveals that the incidence-based $ERR_{1\,Sv}$ is somewhat larger than the mortality-based estimates for most individual cancer sites and organ systems. The EAR is 2.7 times greater for incidence than mortality. Since AR is a function of the ERR, it closely follows the ERR pattern and is about 30% higher in the incidence series than in the mortality series.

A comparison of the estimated number of excess solid tumor cases shows that the incidence-based values are more than twice the corresponding mortality-based values for almost every cancer site. This translates into a sizable difference, depending on which data are used, in the predicted number of excess cases. Approximately 304 excess cancer deaths are predicted based on the mortality series for 1950–1987 compared with 504 excess cancer cases based on the incidence data for 1958–1987 (Tables VIII and IX). For the three periods used in the mortality analysis (1950–1957, 1958–1975, 1976-1987), the predicted numbers of excess deaths are 27.4, 127.9 and 149.2, respectively. In the incidence analysis, there are no data for the first period, but 226.9 and 276.6 excess cases are predicted for the latter two periods.

The differences in the predicted numbers of excess cases are derived largely from the greater excess risk of cancer incidence among women, particularly those who were under age

TABLE IX
LSS Solid Tumor Cases 1958–1987
Distribution of Observed and Fitted Observed Cases by Sex, Time Period, Exposure Status and Age at Exposure

		1958–1975		1976–1987		1958–1987	
Age at exposure	Dose category	<0.01 Gy	0.01–4 Gy	<0.01 Gy	0.01–4 Gy	<0.01 Gy	0.01–4 Gy
				Males			
0–19	Observed cases	53	78	226	212	279	290
	Fitted background	55.44	50.57	203.93	182.06	259.36	232.62
	Fitted excess	0.07	11.46	0.30	40.48	0.38	51.94
20–39	Observed cases	227	187	355	358	582	545
	Fitted background	247.38	219.39	323.68	289.71	571.06	509.11
	Fitted excess	0.13	21.80	0.17	29.15	0.29	50.95
40+	Observed cases	790	766	279	259	1069	1025
	Fitted background	785.52	727.82	285.25	268.20	1070.78	996.02
	Fitted excess	0.22	33.65	0.10	13.52	0.32	47.17
All ages	Observed cases	1070	1031	860	829	1930	1860
	Fitted background	1088.34	997.78	812.86	739.97	1901.20	1737.75
	Fitted excess	0.42	66.91	0.57	83.15	0.99	150.06
				Females			
0–19	Observed cases	115	157	243	274	358	431
	Fitted background	122.43	102.73	239.04	198.86	361.47	301.60
	Fitted excess	0.33	42.29	0.68	80.78	1.01	123.07
20–39	Observed cases	435	479	548	563	983	1042
	Fitted background	445.78	417.24	551.16	508.40	996.94	925.65
	Fitted excess	0.60	72.09	0.75	88.64	1.35	160.73
40+	Observed cases	712	691	303	303	1015	994
	Fitted background	691.80	599.72	314.80	274.54	1006.60	874.26
	Fitted excess	0.44	45.59	0.24	24.06	0.68	69.64
All ages	Observed cases	1262	1327	1094	1140	2356	2467
	Fitted background	1260.02	1119.69	1104.99	981.81	2365.01	2101.50
	Fitted excess	1.37	159.97	1.68	193.48	3.05	353.45
				Both sexes			
All ages	Observed cases	2332	2358	1954	1969	4286	4327
	Fitted background	2348.36	2117.48	1917.85	1721.77	4266.20	3839.25
	Fitted excess	1.79	226.88	2.24	276.63	4.04	503.51

20 years ATB. Among those women, there were 123 excess cancer cases compared with only 42 excess cancer deaths. For men in the same age ATB group, there were 52 excess incident cancer cases and 24 excess cancer deaths. A further look at these data shows that for persons over age 40 years ATB, there is virtually no difference in the incidence and mortality data for either sex. When only the overlapping period (1958–1987) is considered, the differential in the number of excess cancer cases predicted based on incidence or mortality data also is largest for women under age 20 years ATB.

To highlight the differences between incidence and mortality, we plotted the EAR as a function of time since exposure by sex for several ages ATB (Fig. 2). On the basis of the relative risk model, the EARs for females are higher than the EARs for males for persons less than 20 years at the time of exposure. However, the EARs are increasing more rapidly for males than for females at age 20+ ATB. In fact, the difference in the increase is so large that the EARs cross and males have a higher EAR for both incidence and mortality when older. This crossover occurs earlier in the mortality than in the incidence data—at about age 50 for mortality and age 65 for incidence.

Much of the reason for the differences in mortality and incidence-based risk estimates is due to nonfatal breast, thyroid and skin cancers. Together these three sites provide 518 exposed cases or 12% of the total incidence series. These

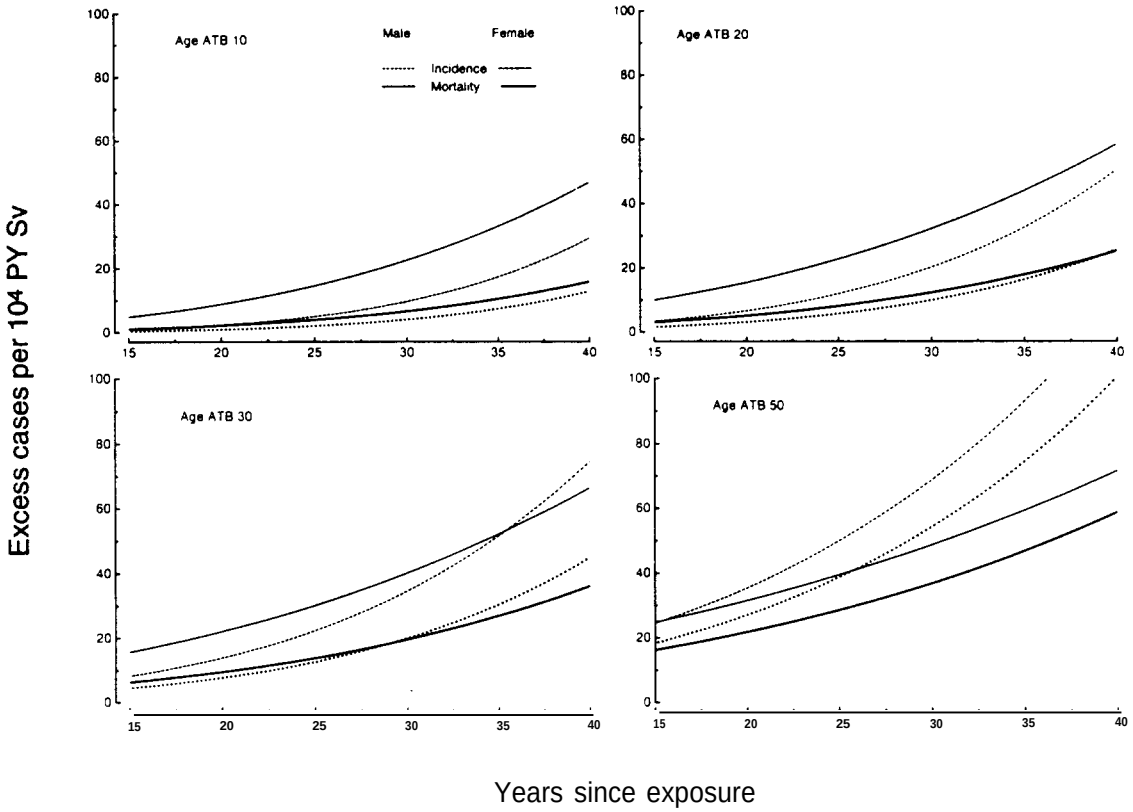

FIG. 2. Comparison of incidence and mortality fitted excess absolute risk (EAR) functions. The plots present fitted estimates of the EAR for cancer incidence and mortality. Fitted curves are given by sex for selected ages at exposure. The estimates are based on time-constant ERR models in which the dose–response function is linear and allowed to vary with sex and age at exposure. The incidence data cover the period from 1958 through 1987. The models used for mortality were fitted to data for the full period, 1950 through 1987, but fitted curves are shown only from 15 years after exposure.

sites are radiosensitive and their combined $ERR_{1\,Sv}$ is high (1.86), i.e., about four times larger than the risk for all other incident cancers combined ($ERR_{1\,Sv}$ = 0.45). Furthermore, cancers of the breast, thyroid and skin exhibit strong effect modification by age at exposure. Their combined $ERR_{1\,Sv}$ for persons under age 20 ATB is 5.53 compared to 0.75 for other cancers. Women have higher ERRs for all solid cancers in both the incidence and mortality series, but the excess for females is more pronounced in the incidence data. While breast cancer accounts for much of the gender difference in the incidence series, women also have higher (nonsignificant) risks of skin and thyroid cancers. The ERR for females for all solid tumors excluding breast, thyroid and skin cancers is 0.61. When these three cancer types are excluded from the incidence analysis, the ERR point estimates are virtually the same for the incidence- and mortality-based series.

A comparison of effect modification in the incidence and mortality data indicates some differences in the two data sets (Table X). Using either incidence or mortality data, females had a higher ERR for all solid tumors combined than males, and the ERR decreased with increasing age at exposure. However, only the incidence data provided evidence for a decreasing ERR with increasing attained age and time since exposure. Similar analyses were done for major cancer sites. For stomach cancer, females had a higher ERR than males in both incidence and mortality, and there was a significant tendency (P = 0.03) for the ERR to decrease with increasing age at exposure in the incidence data, whereas the trend was of only marginal significance in the mortality data (P = 0.06). For colon cancer, there was evidence for a curvilinear response in the mortality data, which was not seen in the incidence data. In addition, the ERR was significantly higher in Hiroshima than in Nagasaki and decreased with increasing age ATB and attained age in the mortality series only. In the incidence series, the ERR decreased with increasing attained age and time since exposure. Females had a highly significantly larger ERR of lung cancer incidence than males, but this difference was not significant in the mortality data. For breast cancer the ERR decreased with increasing age at exposure, whether incidence or mortality data were evaluated. No significant effect modification was detected using incidence or mortality data for cancers of the ovary or bladder.

TABLE X
Effect Modification Based on ERR Model in the LSS Cancer Incidence and Mortality Data

Site/system	Nonlinear dose response[a]	City[b](H:N)	Sex[c](F:M)	Age at exposure	Attained age (adjusted for age at exposure)	Time since exposure (adjusted for age at exposure)
All solid tumors						
Incidence	—	—	▲	▼	▼	▼
Mortality	—	—	▲	▼	—	—
Stomach						
Incidence	—	—	▲	▼	—	—
Mortality	—	—	▲	▽	—	—
Colon						
Incidence	—	△	—	—	▼	▼
Mortality	▲	▲	▽	▼	▼	▽
Liver						
Incidence	—	—	—	—	—	—
Mortality	—	—	—	—	△	—
Lung						
Incidence	—	—	▲	—	—	—
Mortality	—	—	△	—	—	—
Female breast						
Incidence	—	—	N/A	▼	—	—
Mortality	—	—	N/A	▼	—	—
Ovary						
Incidence	—	—	N/A	—	—	—
Mortality	—	—	N/A	—	—	—
Urinary bladder						
Incidence	—	—	△	—	—	—
Mortality	▽	—	—	—	—	—
Legend	▲	Increasing	$P < 0.01$		Decreasing	▼
	▲	Increasing	$0.05 > P > 0.01$		Decreasing	▽
	△	Increasing	$0.10 > P > 0.05$		Decreasing	—
	—		No effect			

[a] Increasing means concave upward while decreasing means concave downward.
[b] Increasing means Hiroshima risk greater than Nagasaki risk.
[c] Increasing means female risk greater than male risk.

DISCUSSION

Since risk estimates derived from the LSS incidence and mortality data are used in the assessment of radiation risks, it is useful to understand how and why these estimates differ depending on whether they are based on incidence or mortality data. Differences in these data stem from many methodological and biological considerations, e.g., completeness of case ascertainment, changes in diagnostic classification over time, accuracy of diagnosis, effectiveness of cancer screening, differences in attained age due to time between diagnosis and death, variable survival for individual cancer types, and improvement in treatment of cancer over time. These factors not only affect the composition of the case series but also strongly influence how the data should be analyzed and interpreted.

For some cancer sites, survival is so good that the use of mortality data is not an option. Others have relatively high survival rates, and therefore there are few cases in the mortality series. For breast cancer the small number of mortality cases limits analyses of the shape of the dose–response curve and effect modification. For salivary, thyroid and nonmelanoma skin cancer, the number of deaths is so small that they have rarely been studied in the context of the LSS mortality studies *(1, 2).*

Site-specific survival patterns can also influence the sex and age distribution of the cancers occurring in the incident and mortality series. In the LSS incidence series, 56% of the cancer cases were diagnosed in women, whereas the corresponding proportion in the mortality data was 52%. This difference is due primarily to the large number of nonfatal incident breast and thyroid cancers. Furthermore, since both of these cancers are highly susceptible to induction by radiation, their inclusion in the incidence data could affect the importance of sex as a potential effect modifier. In the LSS, females had a larger ERR for solid tumors in both the incidence and mortality data, but the level of significance was considerably higher in the incidence data. Similarly, evidence

for a decrease in the ERR with increasing age at exposure was stronger in the incidence data than in the mortality data. The number of cases in those exposed before 30 years of age is larger in the incidence than the mortality data. This would be expected because cases are detected, on average, several years before death. However, an additional consideration is that breast, thyroid and nonmelanoma cancers are types which show strong evidence of an association between early age at exposure and radiation risk. Thus their inclusion in the incidence data would tend to lower the average age ATB of persons in whom excess risks are seen.

For persons who develop cancer and die of the same cancer, length of survival can affect time patterns for risk estimation. For cancers of the esophagus, stomach, colon, rectum, liver, gallbladder, pancreas, lung, uterus, ovary and kidney, as well as lymphoma, multiple myeloma and leukemia, the median survival was less than 1 year. For these cancer types, attained age and time since exposure will be fairly similar whether incidence or mortality data are evaluated. However, for oral cavity, nonmelanoma skin, breast, prostate, bladder, nervous system and thyroid cancers, the median survival time ranged from 15 to 47 months. Thus both attained age and time since exposure will be greater if mortality data are used to study these cancers.

It is difficult to quantify completeness of ascertainment, but the mortality data are deemed close to complete because cases are acquired through the carefully controlled national Koseki system, which maintains continuously updated information on vital status. Incidence data are obtained through monitoring and abstracting hospital records within the tumor registry catchment area, leaving some chance for missed cases. As described in the companion paper on the operation of the tumor registries *(7)*, conventional indices of ascertainment suggest that the Hiroshima and Nagasaki registries are comparable to other cancer registries worldwide, but underascertainment should be expected in any cancer registry.

Because the incidence data are derived from the Hiroshima and Nagasaki tumor registries, case ascertainment is limited to the time and geographic restrictions of these registries. To assess the probable impact of these restrictions, we compared three mortality data sets from the LSS cohort with various time and geographic restrictions. Comparison of these mortality data sets showed virtually no difference in the distribution of cancer deaths by sex, age at exposure, city of exposure, radiation dose or cancer site. Further comparison of the three mortality series showed that of the 484 LSS members dying outside of Hiroshima and Nagasaki during 1958–1987, there was a slightly higher percentage who were originally from Nagasaki and who were exposed to the bomb before age 30. This is consistent with the finding that young people from Nagasaki migrate more frequently than other groups in the LSS *(13)*. Since these differences were taken into account with the migration adjustment, they should have little influence on the incidence data. Furthermore, since only 8% of the cancer deaths during 1958–1987 were outside the catchment area, the number of incident cancer losses is too small to alter the study conclusions substantially.

Thirteen percent of the cancer deaths occurred between 1950–1958. Although 13% is not large, these missed cancers could have an effect on risk estimation if the distribution of cancer types was substantially different from that in later years. Among the 965 LSS cancer deaths reported anywhere in Japan during 1950–1958, more occurred among persons exposed to the bomb after age 40. This would be expected because both background cancer rates and radiation risks are higher at any given time among older people. Thus the similarity, except for age, in the distribution of the mortality cases in the two series with the same geographic, but different follow-up restrictions also suggests that the incidence data findings would not be affected substantially by the period limitation. The most convincing evidence, however, is the similarity of risk estimates obtained in the two mortality series. The higher estimates from the series beginning in 1958 might be explained by a smaller effect of radiation during the first few years after exposure.

Screening programs can have an effect on cancer incidence and age at detection. In Japan, there are screening programs for cancers of the stomach, female breast and cervix. However, the breast and cervical cancer programs do not reach a large proportion of the population. Furthermore, our own analysis of the effects of the AHS biennial clinical examination program shows no major difference in the ERRs for either of these cancer sites. Because screening for stomach cancer is widespread, it may have some influence on the risk estimates. This issue should be considered further. Physicians working in the AHS program are aware of the associations between A-bomb exposure and thyroid cancer and therefore examine their patients carefully. Yet, although the background incidence is two times higher in the AHS survivors than other survivors, the ERR is not dissimilar. Neither background nor excess risks for nonmelanoma skin cancer differed between AHS and non-AHS participants.

A recent evaluation of the accuracy of the underlying cause of death on the death certificate compared to autopsy findings has suggested that about 76% of LSS cancers would be detected based on death certificates and that about 90% of these would be confirmed as cancer *(19)*. However, these figures exhibit significant variation with age at death and place of death. Detection and confirmation rates also vary widely by cancer site and for some sites are unacceptably low. In contrast, the majority (75.4%) of the diagnoses of the incident cancers in this study were verified histologically. In addition, 4.4% were diagnosed by direct visualization and 7.6% were diagnosed clinically. Only 12.6% were based on death certificate diagnoses *(3)*. However, as in the mortality series, there was also variation in the distribution of diagnos-

tic method by cancer site, with the proportion of diagnoses based on death certificate being particularly high (33%) for liver cancer.

This paper highlights the inadequacy of mortality data for studying cancers with relatively good survival such as salivary, skin, breast and thyroid. These cancers are of interest in terms of radiation carcinogenesis because they are readily induced by radiation and because they show strong effects of age at exposure. For most other cancer sites, the number of incident cancers available for analysis was considerably larger than the number of mortality cases. Our analysis also suggests that the overlap of cases between the two series is relatively small. Indeed, because many people with cancer were still alive at the end of the mortality follow-up for more than half of the cancer sites, less than 50% of the individuals with cancers ascertained through the tumor registry died of that same cancer.

Even though the incidence and mortality data sets are dissimilar in many ways, the overall conclusions regarding which solid cancer sites demonstrate a significant dose response generally confirm the mortality findings. Significant excess risks are observed for all solid cancers, and for cancers of the stomach, colon, lung, breast, ovary and urinary bladder when either incidence or mortality data are evaluated. A significant excess of liver cancer is found in both data sets when liver cancer is defined as primary liver cancer or liver cancer NOS on the death certificate. No significant effect of radiation is seen for cancers of the pharynx, rectum, gallbladder, pancreas, nose, larynx, uterus, prostate or kidney in either series. Different results stemming from the two data sets are infrequent. A significant excess of nonmelanoma skin cancer is demonstrated in the incidence data but not in the mortality. Cancers of the salivary gland and thyroid were also in excess in the incidence series, but they were not evaluated in the earlier mortality analyses *(2).* When an ERR model is used, the incidence data provided a point estimate about 40% higher than the mortality data. When an EAR model is used, the point estimate based on incidence data was also larger than the mortality point estimate. For individual cancer sites, the variation between incidence and mortality was sometimes greater.

Compared with the findings for solid tumors, the results for the hematopoietic and lymphatic tumors were less consistent *(8).* Although excess risks of leukemia were found using either incidence or mortality data, and the point estimates were close, significant ERRs and EARs of multiple myeloma were seen in the mortality analysis but not in the incidence analysis. There was also some evidence of an increase in non-Hodgkin's lymphoma among males when incidence data were analyzed but no evidence when the mortality data were analyzed.

The recent completion of comprehensive analyses of cancer incidence data in the LSS cohort provides valuable new information on cancer risks after radiation exposure. While these data are extremely important, they are an additional outcome to be studied and are not a replacement for mortality-based risk estimation. The two types of analyses are complementary, because the end points provide different information and have different problems. The large number of incidence-based cases makes the incidence data particularly useful for evaluating effect modification and comparing site-specific risks. Incidence data are more relevant in terms of cancer etiology because treatment and survival do not influence case ascertainment. With advances in the treatment of cancer, the importance of incidence data will continue to increase. Mortality data are more complete in terms of geographic and time restrictions, describe the course of a tumor once it has occurred, and provide information on the ultimate risk. Both incidence and mortality data have strengths that contribute to their central role in risk estimation.

APPENDIX

In this appendix we present the models used for the computation of the fitted values given in Tables VIII and IX and the curves shown in Fig. 10.

The following notation is used: t, time since exposure; a, attained age; g, age at exposure; s, sex; d, RBE_{10} equivalent dose in sieverts.

As indicated in the expressions below, time since exposure or, where appropriate, its logarithm is centered at 25 years after exposure. Similarly attained age is centered at 50 years. Thus the leading term in the background rate models refers to the risk for a 50-year-old, while the leading term in the excess risk models is an estimate of the risk coefficient in August 1970, i.e., 25 years after exposure. When age at exposure is used as a continuous variable it was centered at age 25. In these cases the leading coefficient describes the risk in 1970 for a person who was 25 years old in 1945. Secular trends in background rate models are written in terms of $(g - 25)$, this is possible because all members of the cohort were exposed at (essentially) the same time. Thus the age-at-exposure covariate is equivalent to 1970 minus the year of birth.

The models used are ERR models of the form

$$\lambda(c,s,g,a)\ [1 + \rho(d)\ \varepsilon(c,s,g,t,a)\ ].$$

Background rates $[\lambda(c,s,g,a)\ ]$ are per 10,000 PY. EAR estimates are computed as the product of the background rate and the ERR $[\rho(d)\ \varepsilon(c,s,g,t,a)\ ]$. These estimates have units of excess cases per 10,000 PY Sv.

Solid Tumor Incidence 1958–1987

Background rate

$$\lambda(s,a,g)=\begin{cases}34.9e^{-0.0047(g-25)+4.94\ln(a/50)-1.20\ln^2(a/50)} & \text{Hiroshima male}\\ 0.08e^{-0.0047(g-25)+4.94\ln(a/50)-1.20\ln^2(a/50)} & \text{Nagasaki male}\\ 0.12e^{-0.0047(g-25)+3.22\ln(a/50)-0.54\ln^2(a/50)} & \text{Hiroshima female}\\ 0.04e^{-0.0047(g-25)+3.22\ln(a/50)-0.54\ln^2(a/50)} & \text{Nagasaki female}\end{cases}$$

Dose response and effect modification

$$\rho(d)\varepsilon(c,s,g,t,a)=\begin{cases}0.54de^{-0.040(g-25)} & \text{male}\\ 0.99de^{-0.040(g-25)} & \text{female}\end{cases}$$

Solid Tumor Mortality 1950–1987

Background rate

$$\lambda(s,a,g)=\begin{cases}19.2e^{-0.00033(g-25)+5.36\ln(a/50)-1.39\ln^2(a/50)} & \text{Hiroshima male}\\ 19.5e^{-0.00033(g-25)+5.36\ln(a/50)-1.39\ln^2(a/50)} & \text{Nagasaki male}\\ 13.9e^{-0.00033(g-25)+3.98\ln(a/50)-0.22\ln^2(a/50)} & \text{Hiroshima female}\\ 14.1e^{-0.00033(g-25)+3.98\ln(a/50)-0.22\ln^2(a/50)} & \text{Nagasaki female}\end{cases}$$

Dose response and effect modification

$$\rho(d)\varepsilon(c,s,g,t,a)=\begin{cases}0.45de^{-0.026(g-25)} & \text{male}\\ 0.77de^{-0.026(g-25)} & \text{female}\end{cases}$$

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